REMARKS

Claims 1-40 were present in the application as filed. In a Preliminary Amendment, claims 1-40 were canceled and new claims 41-60 were added. In response to a restriction requirement, Applicants elected with traverse Group I, claims 41-44, 49-50 and 55-56, drawn to controlled release pharmaceutical compositions containing descarboethoxyloratadine (hereafter, "DCL") and lactose-free carrier.

In the Non-Final Office Action dated November 5, 2003 (hereafter, "Office Action"), the Examiner rejected claims 41-45, 49-51 and 55-57, agreed to additionally examine claims of Group II, claims 45, 49, 51, 55 and 57, drawn to controlled release pharmaceutical compositions containing DCL and a lactose-free carrier, in combination with an analgesic or a decongestant, and pursuant to restriction requirement withdrew claims 46-48, 52-54 and 58-60 from further consideration. The claims now pending in the application are: 41-60. The Examiner's rejections are traversed below.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 41-45, 49-51 and 55-57 under 35 U.S.C. §103(a) as being unpatentable over Villani et al. (US Pat. No. 4,659,716) and Aberg et al. (US Pat. No. 5,731,319), in view of Blaug et al.,[1] Hartauer et al.,[2] the Handbook of Pharmaceutical Excipients,[3] and Remington's Pharmaceutical Sciences.[4]

---

[1] Interaction of Dextroamphetamine Sulfate with Spray-Dried Lactose, J. of Pharma. Sciences, 61 (11), pp. 1770-1775 (1972).
[2] A Comparison of Diffuse Reflectance FT-IR Spectroscopy and DSC in the Characterization of a Drug-Excipient Interaction, Drug. Dev. and Ind. Pharma., 17 (4), pp. 617-630 (1991).
[3] Wade et al., 2nd edition, American Pharma. Assoc. & the Pharma. Press, Royal Pharma. Society of G. Britain, pp. 257-259 (1994).
[4] Genaro et al., 17th edition, Philadelphia College of Pharmacy and Science, pp. 1633-1638 (1985).

The Examiner stated that Villani et al., and Aberg et al. teach DCL in combination with pharmaceutical carriers and excipients. Furthermore, the Examiner asserted that "Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients teach various amine compounds, in high temperature and humidity situations reacting with various sugars, producing a concomitant reduction in active ingredients levels" (Office Action, p. 3, last paragraph). Based on this, the Examiner concluded that "[t]he skilled artisan possessing these teachings would have been motivated to eliminate lactose and sugars from those medicaments containing amine active ingredients, such as those herein claimed" (Office Action, p. 4, first paragraph).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations (*see*, MPEP 2143).

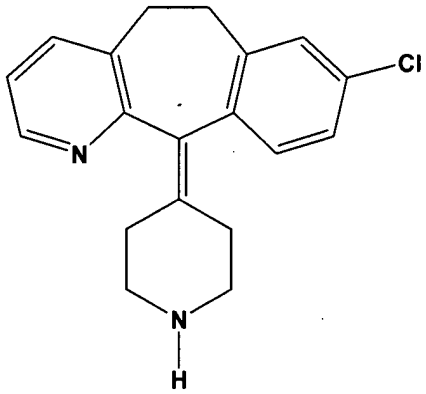
The Applicants respectfully assert that the Examiner has failed to establish a prima facie case of obviousness. Specifically, the cited secondary references of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients, do not suggest or motivate to modify prior art DCL formulations by intentionally excluding lactose from such formulations. This is due to the fact that these secondary references do not teach or suggest that secondary amines, such as DCL, are reactive with lactose.

The attached Declaration of Dr. Sharon M. Laughlin (hereafter, "Declaration") sheds light on the scope of the teaching afforded to a person of skill in the art by the secondary references of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients.

The Declaration states that a person of skill in the art, would take the disclosures of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients as teaching that a primary amine may react with lactose. However, from the teachings of these references, there would be

an expectation that a secondary amine, such as DCL, would not interact with lactose and that lactose-containing DCL compositions would be stable.

As explained in the Declaration, a primary amine is a compound that has a nitrogen atom (N) bound by a covalent bond to only one carbon (C) atom. A secondary amine is a compound that has a nitrogen atom bound by a covalent bond to two carbon atoms. The DCL is a secondary amine since each of its two nitrogen atoms are bound to two carbons as shown below:



Primary and secondary amines represent two distinct species of amine compounds.

The Declaration states that Blaug et al., in the introductory paragraphs, provides a recitation of early thoughts with respect to the incompatibility of amines (with disregard as to species) and lactose. The early investigators recognized that tablets containing amine salts and lactose discolored (turned brown) slowly on storage and concluded that the discoloration was a result of liberation of free amine by basic lubricants in the formulation. In 1965, however, Duvall *et al.* concluded that browning did not depend upon liberation of free amine, but that the lactose/amine interaction was predominantly a *primary amine*-carbonyl type of reaction. The investigation conducted by Blaug (1972) confirmed the conclusions of Duvall et al. that the reaction is "a Schiff base-type [reaction] involving the primary amine and the carbonyl group of the sugar." (page 1772, col. 2 and page 1774, col. 1). Thus, Blaug et al. shows that while the early theory for the browning reaction did not account for amine species, subsequent discoveries did, and concludes that lactose/amine incompatibility was the result of an interaction between

lactose and a primary amine. Therefore, from the disclosure in Blaug et al., one of skill in the art would not expect a secondary amine, such as DCL, to be reactive with lactose.

Furthermore, the Declaration states that Hartauer et al. also teaches that the incompatibility between lactose and amines arose as a result of an interaction between lactose and *primary* amines. Hartauer et al. tested aminophylline, a composition comprised of two molecules of theophylline and one molecule of ethylenediamine. This study compared reactivity of lactose with theophylline, a secondary amine, and ethylenediamine, a primary amine. Hartauer et al. found that while theophylline, a secondary amine, did not interact with lactose, ethylenediamine, a primary amine, did. Thus, Hartauer et al teaches that the primary amines are reactive with lactose while the secondary amines are not reactive with lactose. Therefore, the disclosure in Hartauer et al., would make one of skill in the art expect that a secondary amine, such as DCL, would not be reactive with lactose.

Similarly, as stated in the Declaration, the Handbook of Pharmaceutical Excipients teaches on page 257 that "a Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products." Thus, the Handbook of Pharmaceutical Excipients does not teach incompatibility of lactose with secondary amines.

According to the Declaration, prior to Applicants discovery, DCL was routinely formulated with lactose (see, e.g., Aberg et al. US Pat No. 5,731,319, Examples 7 & 8). This fact demonstrates that there was no recognition of the fact that DCL, a secondary amine, is incompatible with lactose. Moreover, another secondary amine, astemizole, was commercially available from 1988 until 1999 as HISMANAL® tablets (Janssen Pharmaceutica, Inc.) which, according to the *Physician's Desk Reference*, 50th Ed., Medical Economics Co., Montvale, NJ, p. 1293 (1996), contained in each tablet, 10 mg astemizole and lactose in addition to other ingredients. HISMANAL® was removed from the market in 1999 due to safety concerns and not due to astemizole's incompatibility with lactose.

Therefore, the Declaration concludes that Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients do not teach a person of skill in the art that a secondary amine such as DCL may react with lactose.

As evidenced by the Declaration, the state of the art at the time of the invention was such that the person of skill would expect that a secondary amine such as DCL would not interact with lactose and that lactose-containing DCL compositions would be stable. Thus, Applicants' discovery of the incompatibility of lactose and DCL was therefore unexpected and surprising.

The Examiner also cited Remington's Pharmaceutical Sciences reference as teaching coating of the dosage form with an inert coating agent. This reference lacks relevance since, as demonstrated above, the prior art did not recognize the fact that lactose represents a non-inert coating agent for DCL formulations.

Therefore, the Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. Consequently, for all of the above reasons, Applicants respectfully submit that clams 41-45, 49-51 and 55-57 are not obvious.

Conclusion

Reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Edward Timmer, Applicants Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Date of Deposit: April 1, 2004

Edward Timmer
EDWARD TIMMER

Respectfully submitted,

Edward Timmer
EDWARD TIMMER
Attorney for Applicant(s)
Registration No. 46,248

Dated: April 1, 2004

HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579